RESPONSE

I. Status of the Claims

Prior to the second Action, claims 4-9, 23-27, 41 and 49-82 were pending and have been examined (see **Section II**). The second Action is in error in listing claims 4-9, 23-27 and 41-82 as pending (second Action at summary page, page 2), as claims 42-48 were previously canceled. Claims 4-9, 24, 27, 41-71 and 75-82 are now subject to non-final rejection. Claims 23-26 and 72-74 are said to be allowed (see **Section IV**).

Presently, claims 4 and 82 have been amended without prejudice or disclaimer. Claim 83 has been added, which is fully supported by the application as filed and is unified with the examined claims. No claims have been cancelled.

Claims 4-9, 23-27, 41 and 49-83 are therefore in the case. According to 37 C.F.R. § 1.121(c), a copy of the pending claims is provided in the amendment section.

II. All Claims Rejoined

The second Action has withdrawn the earlier six-way restriction requirement and rejoined all pending claims in the case. Applicants appreciate the Action's finding in this regard.

III. Rejections Overcome

The earlier rejections under 35 U.S.C. § 112, second paragraph, 35 U.S.C. § 103(a) and for obviousness-type double patenting have each been overcome, which progress is appreciated. However, in response to the second Action's statement that the earlier rejections "are withdrawn in view of applicant's amendments" (second Action at page 2), Applicants maintain that the withdrawal of the rejections should be viewed in lights of Applicants' response as a whole, including the remarks and submitted documents.

IV. Allowed Claims

In the first Action, each of claims 5, 8-10, 23-26, 41, 57, 58, 61, 62, 64 and 65 were found to be allowable. Many of these allowable claims and their counterparts are now subject to non-final rejection.

The second Action at the summary page indicates that each of claims 23-26 and 72-74 are allowed. As claims 23-26 are dependent on a rejected base claim, Applicants believe that their status is "allowable, but objected to".

Despite the non-final rejections, the present response shows that all pending claims are in condition for allowance.

V. Support for the Claims

Support for the revised claims and the new claim is to be found throughout the specification and claims of the original and parent applications. Any small entity fee necessary for the new dependent claim should be deducted from Peregrine Pharmaceuticals, Inc. Deposit Account No. 50-3493/4001.002299.

Claim 4 has been amended to delete "monoclonal", which was earlier introduced based on the first Action's finding that claim 10, drawn to the use of monoclonal antibodies, was allowable. Present claim 4 thus returns to the language prior to Applicants' first response, and is supported thereby and throughout the specification.

Claim 82 has been amended to add "unconjugated" prior to "antibody", which is supported throughout the specification, as exemplified by claim 68.

New claim 83 is a replacement dependent claim drawn to the use of monoclonal antibodies. This is supported throughout the specification as filed, as exemplified by original dependent claim 10.

It will therefore be understood that no new matter is included within any of the amended or new claims.

VI. First New Double-Patenting Rejection

Claims 4-9, 24, 27, 41-71[1] and 75-82 are newly rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 1-11, 17-20 and 27-54 of U.S. Patent No. 6,783,760 ("the '760 patent"; Attorney Docket No. 3999.002399). Although Applicants respectfully traverse, the Action's concerns are overcome.

At the outset, it is important to note that "the focus of any double patenting analysis necessarily is on the claims in the multiple patents or patent applications involved in the analysis". MPEP 804 (MPEP Eighth Edition, page 800-11, column 2; emphasis added). As the second Action has misinterpreted the claims in the '760 patent, the obviousness-type double patenting rejection has been improperly founded and should be withdrawn.

The second Action takes the position that the '760 patent claims a "method of treating an animal having a vascularized tumor with at least an agent that binds to an aminophospholipid and at least a second anti-tumor agent, wherein the agent is an antibody claimed in the patent" (second Action at page 3, emphasis added). This is in error.

The '760 patent in fact claims methods for treating vascularized tumors by administering at least a first binding ligand that comprises at least a first therapeutic agent operatively attached to a targeting agent that binds to an aminophospholipid, in combination with surgery, radiotherapy or at least a second anti-cancer agent. Thus, all claims of the '760 patent primarily

[1]Note that claims 42-48 are not pending.

require the administration of a therapeutic conjugate, in which a therapeutic agent is delivered to the tumor by attachment to a targeting agent that binds to an aminophospholipid.

In marked contrast, the combination therapy claims of the present application all rely on the administration of a naked or unconjugated antibody.

An obviousness-type double patenting rejection is analogous to a failure to meet the nonobviousness requirement of 35 U.S.C. § 103, and such rejections therefore require application of the guidelines for § 103(a) rejections, as embodied in *Graham v. John Deere Co.*, 148 USPQ 459 (U.S.S.Ct. 1966). MPEP 804 (MPEP Eighth Edition, page 800-22, columns 1 and 2). There is nothing in the claims of the '760 patent, which all require a conjugate that delivers an exogenous therapeutic agent, to teach or suggest the successful administration of a naked antibody lacking an attached therapeutic agent. Indeed, the specification explains that the present invention:

> "...embodies the unexpected discovery that naked antibodies against aminophospholipid components are capable of specifically inducing tumor blood vessel destruction and tumor necrosis *in vivo*. Certain preferred aspects of the invention were developed from the surprising discovery that antibodies against the aminophospholipid, phosphatidylserine (PS), specifically localize to the vasculature of solid tumors and, even more surprisingly, exert a tumor destructive effect in the absence of conjugation to effector molecules, such as toxins or coagulants. Single component therapeutics directed against aminophospholipids thus represent a breakthrough in vascular targeting and provide safe and effective methods for the treatment of solid tumors."
>
> Specification at first and second paragraphs of 'Summary of the Invention'.

Accordingly, the proposed rejection fails to meet the established criteria for legal obviousness and a proper *prima facie* case of obviousness-type double patenting has not been made.

The first obviousness-type double patenting rejection is therefore overcome and should be withdrawn[2].

VII. Second New Double-Patenting Rejection

Claims 4-9, 41, 49-51, 53, 57, 58, 61, 68-71, 75-78 and 80-82 are also newly rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 4-11, 28, 29 and 43 of U.S. Patent No. 6,312,694 ("the '694 patent"; Attorney Docket No. 3999.002300). Although Applicants respectfully traverse, the Action's concerns are overcome.

The '760 patent discussed above is a continuation of the '694 patent cited in the instant rejection. The claims in the '694 patent are also limited to the administration of a therapeutic conjugate, in which a therapeutic agent is delivered to the tumor by attachment to a targeting agent that binds to an aminophospholipid[3]. There is nothing in the claims of the '694 patent to teach or suggest the successful administration of a naked antibody lacking an attached therapeutic agent.

Applicants therefore respectfully incorporate by reference all reasoning set forth above in response to the first obviousness-type double patenting rejection. In light thereof, the proposed rejection fails to meet the established criteria for legal obviousness and a proper *prima facie* case of obviousness-type double patenting has not been made.

The second obviousness-type double patenting rejection is therefore overcome and should be withdrawn[2].

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[2]This does not preclude Applicants from submitting a Terminal Disclaimer and the appropriate fee should one or more obviousness-type double patenting rejections become the only remaining issues in the case.

[3]The '694 patent does not claim administration of a conjugate that binds to an aminophospholipid "and at least a second anti-tumor agent" (second Action at page 3), other than the administration of two distinct conjugates that each bind to an aminophospholipid.

VIII. New Rejection Under 35 U.S.C. § 103(a)

Claims 4, 6, 7, 9, 25, 41, 49, 50, 57, 58, 61, 64, 65, 67, 68, 71, 73, 75-78 and 80-82 are newly rejected under 35 U.S.C. § 103(a) as allegedly being legally obvious over U.S. Patent No. 6,300,308 to Alan J. Schroit ("Schroit") in combination with U.S. Patent No. 5,725,856 to Hudziak *et al.* ("Hudziak"). Although Applicants respectfully traverse, the Action's concerns are overcome.

A. The Rejection is *Prima Facie* Improper and Overcome

For an obviousness rejection to be proper under 35 U.S.C. § 103(a), it is required that the cited prior art suggest to those of ordinary skill in the art that they should make the claimed composition or device, or carry out the claimed process; and that the prior art also convey to those of ordinary skill a reasonable expectation of success. *In re Dow Chemical Co.*, 5 USPQ 2d 1529, 1531 (Fed. Cir. 1988). Both the suggestion and the reasonable expectation of success must be founded in the prior art, not in the applicant's disclosure. *Id.*

The presently claimed invention is drawn to methods of treating an animal having a vascularized tumor by administering at least a first antibody, or an antigen-binding fragment thereof, that binds to an aminophospholipid on the luminal surface of blood vessels of the vascularized tumor and at least a second therapeutic agent, as defined in the claims.

Schroit is cited as disclosing methods for using lipid-specific antibody compositions, including antibodies specific for PS, to treat cancer, wherein the cancer is characterized by the presence of PS on the external leaflet of the tumor (second Action at page 4). Schroit is further said to teach that the antibodies may be used simultaneously in combination with a second anti-cancer agent such as diphtheria toxin (second Action at page 4). The second Action has mischaracterized Schroit in these respects.

Schroit does not teach or suggest the administration of anti-PS antibodies, either alone or in any combination. Rather, Schroit concerns immunization with PS-polypeptide conjugates to generate PS-specific antibodies.

Moreover, Schroit at column 8 does not teach the administration of antibodies "simultaneously in combination with a second anti-cancer agent such as diphtheria toxin" (second Action at page 4). Rather than teaching the administration of diphtheria toxoid as a second anti-cancer agent, Schroit at column 8, lines 58-67 teaches that, with respect to preparing lipid-specific antibodies, "it is necessary to boost the host immune system", which may be achieved by coupling the lipid of interest to a carrier. Diphtheria toxoid is set forth as one example of such a carrier, along with KLH, BSA, β2-glycoprotein I, albumins such as ovalbumin, mouse serum albumin or rabbit serum albumin, and bovine gamma globulin (Schroit at column 8, lines 58-67). Thus, the diphtheria toxoid of Schroit is a carrier that is conjugated to a "lipid of interest" for use in lipid immunization, and is not administered separately as a second anti-cancer agent.

Although the second Action correctly cites Schroit as disclosing that "cancer is characterized by the presence of PS on the external leaflet of the tumor" (second Action at page 4), this does not support the § 103(a) rejection. In common with Fishman cited in the first Action, Schroit's indication of PS expression on tumor cells does not teach or suggest the presently claimed invention, where the targeted aminophospholipids were surprisingly discovered to be present on the luminal surface of blood vessels of the vascularized tumor, *i.e.*, on normal cells.

Indeed, by disclosing that PS may appear at the surface of tumor cells, as opposed to the situation in normal cells (Schroit throughout, *e.g.*, column 16, lines 27-33), Schroit teaches away

from the present invention. As the present invention targets aminophospholipids on the luminal surface of the normal cells of the tumor blood vessels, and as Schroit teaches that PS is not expressed at the surface of normal cells, the present invention proceeds contrary to Schroit, which is further evidence of patentability.

By concerning tumor cells, rather than tumor vasculature, Schroit matches Fishman again, and both represent the problematic art of tumor cell targeting, discussed in the background section of the present specification. Both chemotherapeutics and immunotoxins against tumor cells are limited by tumor cell resistance, leading to antigen-negative or antigen-deficient tumor cells, which can survive and repopulate the tumor or lead to further metastases (specification at background). The poor accessibility of tumor cells is another limitation in therapies aimed at tumor cells. The tumor mass is generally impermeable to molecules of the size of antibodies and immunotoxins, such that the physical diffusion distances and the interstitial pressure within the tumor are significant limitations to therapies aimed at tumor cells (specification at background).

The present inventors developed vascular targeting methods for tumor treatment, at least in part, to overcome the many drawbacks associated with targeting immunotoxins to cancer cells. The new finding that PS is a marker of the normal cells of the tumor vasculature thus provides effective therapies that overcome the problems associated with tumor cell targeting, such as tumor cell resistance, antigen escape and effective penetration into the tumor.

Applicants appreciate the second Action's finding that Schroit does not teach methods of treating cancer using an anti-PS antibody in combination with other chemotherapeutic or anti-angiogenic agents (second Action at page 4). Nonetheless, the second Action relies on Hudziak in an attempt to cure the admitted deficiencies of Schroit. Even if properly combined with

Schroit, Hudziak not only fails to cure the deficiencies of Schroit, but itself further teaches away from the invention.

Although Applicants elect to address the combination of Schroit and Hudziak, this is not an acquiescence that the proposed combination is legally proper. Rather, it is clear that Schroit and Hudziak, even if properly combined, fail to teach or suggest the claimed invention and, in fact, teach away from the invention. Notably, as with Fishman and Tschmelitsch in the first Action, Schroit and Hudziak share the fundamental defect of failing to teach or suggest any aspect of targeting the blood vessels of a vascularized tumor, an important feature of claimed invention.

The second Action cites Hudziak as teaching a method of inhibiting the growth of tumor cells that over-express a growth factor receptor by administering antibodies, either alone or in combination with other cytotoxic factors (second Action at page 4). In particular, the second Action cites Hudziak as teaching that a cytotoxic factor exerts a cytostatic and cytotoxic effect, and refers to exemplary chemotherapeutic drugs and an anti-angiogenic agent (second Action at page 5).

Hudziak does not teach or suggest administering an anti-aminophospholipid antibody, either alone or in combination, to treat a vascularized tumor. Hudziak particularly fails to teach or suggest administering an antibody that binds to an aminophospholipid on the luminal surface of blood vessels of the vascularized tumor, whether alone or in combination with a second anti-cancer agent. Hudziak thus markedly fails to cure the deficiencies of Schroit. Furthermore, Hudziak itself teaches away from the claimed invention.

Importantly, Hudziak is limited to methods of inhibiting the growth of <u>tumor cells</u>. Not only tumor cells, but tumor cells that over-express a growth factor receptor (Hudziak at abstract),

particularly the HER2 receptor (Hudziak, claims). Aside from focusing on HER2, Hudziak thus still represents the old and problematic field of tumor cell targeting, the many drawbacks of which (*e.g.*, survival of antigen-deficient cells and tumor impermeability) are overcome by the present invention.

There is nothing in Hudziak to teach or suggest any aspect of targeting the blood vessels of a vascularized tumor, as in the presently claimed invention. Hudziak, even in combination with Schroit, does not teach or suggest alternatives to tumor cell targeting, and particularly fails to teach or suggest targeting any component, let alone an aminophospholipid, expressed on the luminal surface of blood vessels of a vascularized tumor. Schroit and Hudziak thus fail to raise a *prima facie* concern under § 103(a).

The second Action further alleges that it would be *prima facie* obvious to one of ordinary skill in the art at the time the invention was made "to combine a chemotherapeutic or anti-angiogenic agents with antibodies" (second Action at page 5, emphasis added). However, the presently claimed invention is not drawn to the combination of a chemotherapeutic or anti-angiogenic agent "with antibodies", but to methods for treating vascularized tumors by administering an antibody, or antigen-binding fragment thereof, that binds to an aminophospholipid on the luminal surface of blood vessels of the vascularized tumor, in combination with a particular chemotherapeutic, anti-angiogenic or therapeutic agent as defined in the claims. The second Action is thus ignoring the claimed invention as a whole, which is improper in an obviousness analysis. *In re Wright*, 6 USPQ 2d 1959, 1962 (Fed. Cir. 1988).

The second Action continues to allege that it is well known that chemotherapeutics or anti-angiogenic agents "can be used in combination with antineoplastic antibodies to achieve an additive effect" (second Action at page 5; emphasis added). This again highlights that the cited

art is confined to the old attempts to target and control the neoplastic tumor cells, with all the attendant limitations, and does not teach or suggest the innovative tumor vascular targeting of the present invention. As to the alleged motivation to achieve an additive effect (second Action at page 5), Applicants respectfully refer to Exhibit B attached to their first response, which shows the surprising and synergistic effects achieved by a combination therapy of the present invention.

Indeed, the present invention, unlike the cited art, provides for the intelligent selection of second anti-cancer agents for use with the anti-aminophospholipid antibodies (see, *e.g.*, specification from page 32, line 11 to page 33, line 12; and Section J). For example, the specification teaches the administration of a second anti-cancer agent *prior* to the anti-aminophospholipid antibody to increase aminophospholipid expression, or injure or induce apoptosis in the tumor blood vessel endothelium (specification at page 33, lines 5-12); and the administration of a second anti-cancer agent *subsequent* to the anti-aminophospholipid antibody to kill tumor cells or as an anti-angiogenic agent that inhibits metastasis of tumor cells (specification from page 32, line 27 to page 33, line 3). No such teaching or suggestion exists in the cited art.

The § 103(a) rejection is thus *prima facie* improper on various grounds, including that Schroit has been mischaracterized, that neither Schroit nor Hudziak teaches or suggests targeting the blood vessels of vascularized tumors, and that the art teaches away from the claimed invention.

B. Schroit is Removed Under 35 U.S.C. § 103(c)(1)

In any event, the alleged obviousness rejection is *prima facie* improper and overcome as Schroit is removed under 35 U.S.C. § 103(c)(1).

The present application has a priority date of July 13, 1998. Schroit issued on October 09, 2001. Schroit is thus only potentially available as prior art under 35 U.S.C. § 102(e). Indeed, this is evidenced in the second Action, which cites Schroit with a date of "12/31/1997", the date of the provisional application to which Schroit claims priority (second Action at page 4).

Schroit is not available for citation as part of a § 103(a) rejection, because Schroit is removed from consideration as a commonly owned patent under 35 U.S.C. § 103(c)(1). All three criteria for removing Schroit under 35 U.S.C. § 103(c)(1) are met, namely:

(1) the present application was filed on or after November 29, 1999 (filed November 30, 2001);

(2) the subject matter of the Schroit patent qualifies as prior art for § 103(a) only under one or more of 35 U.S.C. §§ 102(e), (f) or (g); and

(3) the subject matter of the Schroit patent and the presently claimed invention were, at the time the claimed invention was made, subject to an obligation of assignment to the same person (entity), *i.e.*, Board of Regents, The University of Texas System.

C. Statement of Common Ownership

According to MPEP 706.02(l)(2), Applicants hereby state, in a clear and conspicuous manner, that Application Serial No. 09/998,833 and U.S. Patent No. 6,300,308 were, at the time the invention of Application Serial No. 09/998,833 was made, subject to an obligation of assignment to Board of Regents, The University of Texas System.

In addition, the common ownership is evidenced by the assignments already recorded in the U.S. Patent and Trademark Office.

D. § 103(a) Conclusion

The new § 103(a) rejection is therefore overcome and should be withdrawn.

IX. Conclusion

This is a complete response to the referenced Official Action. In conclusion, Applicants submit that, in light of the foregoing remarks, the present claims are in condition for allowance. Should Examiner Fetterolf have any questions or comments, a telephone call to the undersigned Applicants' representative is earnestly solicited.

Respectfully submitted,

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